April 06, 2007

Roger Citron, R.Ph.
DPHHS
PO Box 202951
Helena, MT 59620-2951

Dear Dr. Citron:

Your Senior Regional Scientific Manager, Kate Ryan, has forwarded your request for information regarding TOPROL-XL® (metoprolol succinate) Extended-Release Tablets. Included for your review is the requested 2-page overview of TOPROL-XL.

The above information is supplied to you as a professional courtesy in response to your request. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. Prescription drugs used outside of their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. AstraZeneca does not recommend the use of TOPROL-XL in any other manner than as described in the enclosed prescribing information. We hope that you find this information useful. Please complete and return the enclosed survey to help us determine how well we are meeting your expectations. The survey can also be completed online at http://mrsurvey.astrazeneca-us.com.

Thank you for your interest in TOPROL-XL® (metoprolol succinate) Extended-Release Tablets. If we may be of further assistance to you, please contact AstraZeneca at 1-800-236-9933.

Tel 800 236 9933
Fax 302 885-1400
www.astrazeneca-us.com

Medical Resources FOC/CE1, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437

Sincerely,

Debra A. Henn, Pharm.D.

Senior Medical Information Manager

Enclosure(s):

- TOPROL-XL Prescribing Information.
- Batisky DL, Sorof JM, Sugg J, et al. *J Pediatr*. 2007;150:134-139.
- Falkner B, Francos G, Kushner H. *J Clin Hypertens*. 2006;8:336-343.
- Frishman WH, Hainer JW, Sugg J. *AJH*. 2006;19:388-395.
- Papademetriou V, Hainer JW, Sugg J. *Am J Hypertens*. 2006;19:1217-1225.

INQ 602353

Summary for TOPROL-XL (metoprolol succinate) for Montana Medicaid (April 2006-March 2007)

TOPROL-XL is a once-daily beta-$_1$ selective lipophilic adrenoreceptor-blocking agent indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Metoprolol succinate is also indicated in the long-term treatment of angina pectoris, and for the treatment of stable, symptomatic (New York Heart Association Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin.[1] *Please see accompanying full prescribing information for TOPROL-XL.*

Use in Special Populations

Use in Pediatrics

In a 4-week, double-blind, placebo-controlled, dose ranging study the safety and efficacy of extended release metoprolol succinate (metoprolol XL) in patients aged 6 to 16 years with confirmed hypertension was evaluated.
[1] After a 1- to 2- week single blind, placebo run-in period, 140 eligible subjects were randomized to metoprolol XL 0.2 mg/kg, 1 mg/kg, 2 mg/kg or placebo in a 1:2:2:1 fashion. Metoprolol XL significantly reduced sitting systolic blood pressure (SiSBP) when dosed (mean±SD) at 1.0 mg/kg (7.7±8.6 mmHg), 2.0 mg/kg (6.3±9.0 mmHg), and when all doses were pooled (6.1±8.7 mmHg) ($p<0.05$). The decline in sitting diastolic blood pressure (SiDBP) showed significant dose response with metoprolol XL at the 2 mg/kg dose (7.5±9.0 mmHg) ($p=0.017$). Reductions in standing BP measurements were similar to sitting BP measurements. In the 4-week study, one patient on placebo discontinued study treatment due to an adverse event (upper respiratory infection). The average heart rate was increased with placebo (5.4 beats per minute [BPM]), and decreased with ER metoprolol (the maximum decrease was –6.5 BPM at 1.0 mg/kg).

One hundred patients initially randomized in the 4-week study completed a subsequent 52-week open-label trial. The open-label period was designed to report on safety outcomes, and to determine the efficacy of study medication by response rates. The mean dose±SD at study entry was 37±33 mg, 97±64 mg at week 16, and 112±69 mg at the end of the study. Upon entry into the open-label study, 41% of the patients were classified as a "responder." The response rate increased to 64% at the end of the study. Metoprolol XL was well tolerated, with a 5% discontinuation rate at 1 year. The majority of events were considered mild to moderate. There were no clinically meaningful laboratory or electrocardiogram changes.

Use in Diabetes

The metabolic effects of metoprolol XL were examined to determine its effect on insulin sensitivity in 30 nondiabetic patients with hypertension.[2] Both untreated patients and patients currently taking antihypertensive medications were eligible for the study unless the patient required 3 or more medications for blood pressure control. For 14 days, patients received single-agent antihypertensive therapy with hydrochlorothiazide (HCTZ) 12.5 mg daily. Then patients whose blood pressure was still >140/90 mm Hg underwent an insulin clamp procedure to quantify insulin sensitivity at baseline. Subsequently, metoprolol XL 50 mg daily was started and titrated every 2 weeks to a dose that lowered blood pressure to <140/90 mm Hg (maximum dose of 200 mg/day). Results from an insulin clamp procedure showed no statistically or clinically significant changes in measures of insulin sensitivity between HCTZ therapy alone and metoprolol XL plus HCTZ therapy. Additionally, no statistically significant changes in insulin sensitivity estimates or in HbA1c were observed. Statistically significant decreases in plasma cholesterol and low-density lipoprotein cholesterol were seen with metoprolol XL plus HCTZ therapy ($p<0.01$).

Comparative and Concomitant Use Trials

MFACT

A randomized, double-blind, placebo-controlled, parallel group, unbalanced-factorial study was conducted to evaluate once daily dosing of metoprolol XL, ER felodipine, ER felodipine/metoprolol XL combination and placebo in adults with essential hypertension.[3] After a 4- to 5-week placebo run-in period, 1092 eligible patients entered a 9-week double-blind treatment period, followed by a 2-week double blind, down titration period. Patients (age 18-80 years) were randomized to one of 16 treatment groups: metoprolol XL 25, 100, or 400 mg; ER felodipine 2.5, 10, or 20 mg; ER felodipine/metoprolol XL 2.5/25, 2.5/100, 2.5/400, 10/25, 10/100, 10/400, 20/25, 20/100, or 20/400 mg; or placebo. The primary efficacy measure (SiDBP) declined from baseline to week 9 in all treatment groups, mainly in a dose-dependent and monotonic manner (Table I). Combination therapy with metoprolol XL and ER felodipine was more effective than monotherapy and placebo, generally with additive effects. In a pairwise comparison, each of the nine ER felodipine-metoprolol XL combinations was more effective in lowering SiDBP than the individual components ($p<0.05$) for all with the exception of the ER felodipine 20 mg/metoprolol XL 25 mg combination versus ER felodipine 20 mg (data not shown). Similar findings were noted for SiSBP, as blood pressure declined with all treatments. The decline with the individual therapies tended to be dose-related and monotonic, the only exception being metoprolol XL 100 mg. Combination therapies were again more effective than their components. The results for standing blood pressure were similar to those for sitting blood pressure, and no notable acute postural decline in mean blood pressure was observed. Commonly reported adverse events included headache (21%), peripheral edema (20%), fatigue (7%), and dizziness (6%). A total of 119 patients discontinued treatment due to an adverse event. The largest adverse event discontinuation rates occurred in the medium to high dose ER felodipine monotherapy (19% for 10 mg; 21% for 20 mg) and in combination with metoprolol XL treatment groups. The most common adverse events leading to study drug discontinuation were peripheral edema (4%) and headache (2%), and fatigue (1%).

TABLE I: Observed and Adjusted (ANCOVA) Mean Change from Baseline to Visit 9 (intent-to-treat population) in SiDBP (mm Hg). Adapted from *AJH*. 2006;19:391.

Treatment group	n	Baseline, mean (range)	Observed change, mean (range)	Adjusted change*
Placebo	95	99.3 (95 to 111)	-4.1 (-27 to 19)	-4.0
Metoprolol XL				
25 mg	88	99.7 (95 to 111)	-8.1 (-30 to 9)	-7.7
100 mg	44	99.3 (95 to 109)	-9.2 (-21 to 10)	-9.4
400 mg	90	100.3 (95 to 112)	-11.7 (-36 to 15)	-11.1
ER felodipine				
2.5 mg	93	100.3 (95 to 111)	-7.8 (-31 to 19)	-7.7
10 mg	46	100.2 (95 to 110)	-9.2 (-24 to 4)	-8.7
20 mg	89	99.7 (95 to 113)	-12.1 (-36 to 6)	-11.8
ER felodipine/metoprolol XL				
2.5/25 mg	88	99.6 (95 to 110)	-10.8 (-27 to 6)	-11.0
10/25 mg	45	99.6 (95 to 111)	-12.5 (-39 to –1)	-12.3
20/25 mg	43	99.7 (95 to 111)	-13.5 (-29 to 4)	-13.7
2.5/100 mg	51	99.1 (95 to 112)	-13.6 (-29 to –4)	-13.4
10/100 mg	93	100.3 (95 to 111)	-13.5 (-32 to 3)	13.4
20/100 mg	47	100.8 (95 to 113)	-14.8 (-34 to 1)	-14.6
2.5/400 mg	46	99.9 (95 to 111)	-14.5 (-29 to 0)	-14.2
10/400 mg	45	100.2 (95 to 114)	-16.5 (-28 to 3)	-16.5
20/400 mg	84	100.2 (95 to 112)	-15.8 (-42 to 13)	-15.2
Total	1087			

ANCOVA= analysis of covariance; ER= extended-release; SiDBP = sitting diastolic blood pressure. *Adjusted by analysis of covariance.

ATTACH

The ATTACH (Assessment of TOPROL-XL Taken in Combination with Hydrochlorothiazide) trial was a multicenter, double-blind, placebo-controlled, unbalanced, factorial clinical trial, including 1571 patients with essential hypertension.[4] After a 4- to 5-week single blind, placebo run in period, patients were randomized to treatment with 4 dose levels of metoprolol XL (25 mg, 50 mg, 100 mg, and 200 mg), 3 dose levels of HCTZ (6.25 mg, 12.5 mg, and 25 mg) and 9 dose levels of the combinations for 8 weeks. The primary antihypertensive efficacy for SiDBP and SiSBP (for at least one combination) was greater for both measures (p=0.0015 and 0.0006 respectively). The blood pressure changes with HCTZ, metoprolol XL, and their combination were additive and dose related. Pairwise comparisons of all combinations showed greater SiDBP and SiSBP reductions when compared with placebo (p<0.001) (Table II). The study treatments were well tolerated as only 2.9% of subjects discontinued treatment due to an adverse event. Headache was the most commonly reported adverse event (6.2% in the treatment groups vs. 9.2% in the placebo group). Serum potassium levels decreased with increasing doses of HCTZ, and increased with higher doses of metoprolol XL. The heart rate decreased with increasing doses of metoprolol XL, but not change with HCTZ.

TABLE II. Mean Change from Baseline in SiSBP and SiDBP. Adapted from *Am J Hypertens.* 2006;19:1221.

Treatment	n	SiDBP		SiSBP	
		Change (mm Hg)	95% CI	Change (mm Hg)	95% CI
Placebo	152	-4.27	-5.60, -2.95	-2.76	-4.91, -0.61
Metoprolol XL 25 mg	89	-7.73	-9.46, -5.99	-9.11	-11.93, -6.30
Metoprolol XL 50 mg	93	-8.89	-10.59, -7.19	-9.39	-12.14, -6.64
Metoprolol XL 100 mg	95	-9.12	-10.80, -7.44	-8.61	-11.33, -5.89
Metoprolol XL 200 mg	51	-12.49	-14.78, -10.2	-13.01	-16.72, -9.30
HCTZ 6.25 mg	86	-8.19	-9.95, -6.43	-8.72	-11.58, -5.86
HCTZ 12.5 mg	104	9.66	-11.26, -8.05	-9.84	-12.44, -7.24
HCTZ 25 mg	48	-9.40	-11.76, -7.04	-13.72	-17.54, -9.89
Metoprolol XL / HCTZ 25/6.25 mg	144	-7.71	-9.07, -6.35	-7.92	-10.13, -5.72
Metoprolol XL / HCTZ 25/12.5 mg	141	-9.93	-11.31, -8.55	-12.32	-14.55, -10.09
Metoprolol XL / HCTZ 50/6.25 mg	136	-10.06	-11.46, -8.65	-12.82	-15.09, -10.55
Metoprolol XL / HCTZ 50/12.5 mg	147	-10.86	-12.21, -9.51	-12.59	-14.78, -10.40
Metoprolol XL / HCTZ 100/6.25 mg	45	-12.75	-15.19, -10.32	-12.07	-16.02, -8.11
Metoprolol XL / HCTZ 100/12.5 mg	94	-13.52	-15.21, -11.83	-17.12	-19.85, -14.38
Metoprolol XL / HCTZ 100/25 mg	42	-13.55	-16.07, -11.02	-16.60	-20.69, -12.51
Metoprolol XL / HCTZ 200/12.5 mg	43	-12.76	-15.26, -10.26	-17.30	-21.34, -13.26
Metoprolol XL / HCTZ 200/25 mg	49	-16.46	-18.80, -14.13	-18.61	-22.40, -14.82

SiDBP = sitting dostolic blood pressure; SiSBP = sitting systolic blood pressure; CI = Confidence Interval; HCTZ = Hydrochlorothiazide

Reference(s):

[1] TOPROL-XL Prescribing Information.

[2] Batisky DL, Sorof JM, Sugg J, et al. *J Pediatr*. 2007;150:134-139.

[2] Falkner B, Francos G, Kushner H. *J Clin Hypertens*. 2006;8:336-343.

[3] Frishman WH, Hainer JW, Sugg J. *AJH*. 2006;19:388-395.

[4] Papademetriou V, Hainer JW, Sugg J. *Am J Hypertens.* 2006;19:1217-1225.

Medical Resources Quality Assurance Survey

Inquiry Number: 602353

Product: TOPROL-XL

Dear Dr. Roger Citron,

We hope that the data provided to you proved useful. Please take a few minutes to answer the following questions in order to help us determine how well we are meeting expectations. This survey can be:

- Completed online at http://mrsurvey.astrazeneca-us.com/ with the Inquiry Number listed above.
- Filled out and faxed back to Medical Resources at (800) 640-5886 OR (302) 885-1400.
- Filled out and mailed back to AstraZeneca at:
  Medical Resources FOC/CE1-706
  1800 Concord Pike
  P.O. Box 15437
  Wilmington, DE 19850-5437

Adverse Events Reporting

Clinicians are encouraged to report suspected adverse events to AstraZeneca by calling 1-800-236-9933

ADVERSE EVENTS SHOULD NOT BE REPORTED USING THIS FORM

1. Did the response answer your question? ❑ Completely ❑ Partially ❑ Not at all

   If you checked "Partially" or "Not at all", please explain:

2. Using the scale below, please rate the following statements concerning the response from AstraZeneca to your inquiry.

	Strongly Agree	Agree	Slightly Agree	Slightly Disagree	Disagree	Strongly Disagree
The information is useful / helpful	❑	❑	❑	❑	❑	❑
The information is clear and logical / understandable	❑	❑	❑	❑	❑	❑
The information is balanced	❑	❑	❑	❑	❑	❑
Our response to your inquiry was handled in a reasonable amount of time / timely response	❑	❑	❑	❑	❑	❑
3. Overall, I was satisfied with the quality of the information I received.	❑	❑	❑	❑	❑	❑

4. In general, how do the responses from AstraZeneca compare to those of other companies?	Superior	Above Average	Average	Below Average	Inferior	Not enough experience to compare
	❑	❑	❑	❑	❑	❑

5. What is your profession?	Physician	Pharmacist	Nurse	Physician Assistant	Other
	❑	❑	❑	❑	❑

6. Please provide any suggestions for changes or improvement in the medical information service provided by AstraZeneca in the space below:

Thank you for taking the time to complete the survey. We hope to use this information to continually improve our services.